REMARKS

In the Office Action, claims 6 and 23-24 are rejected under 35 U.S.C. §112, first and second paragraphs. Claim 6 has been amended Applicants believe that the rejections have been overcome or are improper in view of the amendments and at least for the reasons set forth below.

At the outset, the Patent Office has objected to the specification as indicated on page 2 of the Office Action. In response, Applicants have amended the specification as previously discussed and thus believe that they have been responsive to the Patent Office's comments. Applicants note for the record that these changes were made for clarification purposes and thus should not be deemed to narrow and/or disclaim claimed subject matter in view of same.

In the Office Action, claims 6 and 23-24 are rejected under 35 U.S.C. §112, second paragraph. The Patent Office alleges that claim 6 is vague and indefinite in that it is ambiguous whether the nutritional composition as a whole is administered in an amount of about 2 g per day to about 15 g per day or whether this is the amount of dextran provided in the composition. Further, the Patent Office alleges that the claim term "increasing insulin sensitivity" is indefinite. See, Office Action, page 2.

As previously discussed, independent claim 6 has been amended. As amended, claim 6 recites, in part, that dextran is administered in an amount from about 2g per day to about 15g per day. Support for this amendment can be found in the specification, for example, on page 5 at lines 4-5. Thus, the allegation that claim 6 is vague and indefinite with respect to the administration in an amount of about 2 g per day to about 15 g per day should be resolved.

With respect to the claim term "increasing insulin sensitivity", Applicants believe that this term is clear in meaning and scope as further supported in the specification. Indeed, this term is referred to on page 1 of the specification. Clearly, this suggests that one skilled in the art should readily understand the scope and meaning of this term as claimed. Therefore, Applicants believe that claims 6 and 23-24 are clearly defined as further supported in the specification and thus comply with the requirements pursuant to 35 U.S.C. §112, second paragraph.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

In the Office Action, claims 6 and 23-24 are rejected under 35 U.S.C. §112, first paragraph. The Patent Office alleges that there is no basis or support in the present specification for the recitation in claim 6 of enterally administering a nutritional composition comprising

dextran having a molecular weight above about 500,000 and that is administered in an amount from about 2g per day to about 15g per day. As amended, claim 6 now recites, in part, that dextran is administered in an amount from about 2g per day to about 15g per day.

Contrary to the Patent Office's position, Applicants believe that the specification as originally-filed provides sufficient support and basis for the subject matter as claimed in claim 6. For example, the specification provides that the enteral administration of dextran provides a convenient and simple way of selectively increasing the production of propionate in the gastro-intestinal tract. See, specification, page 3, lines 3-5. Dextran is a high molecular weight dextran, such as above about 500,000. See, specification, page 3, lines 11-13. The amount of dextran that the patient receives is preferably in the range of about 2g to about 15g per day. See, specification, page 5, lines 4-5. Therefore, Applicants believe that the written description requirement has been satisfied pursuant to 35 U.S.C. §112, first paragraph.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

In the Office Action, claims 6 and 23-24 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement. Applicants believe this rejection is improper for at least those reasons set forth below.

The present invention is based on the discovery that fermentation of dextran by micro-organisms in the gastro-intestinal tract results in the production of relatively higher amounts of propionate as compared to other non-digestible polysaccharides. Thus, as propionate is a physiologic modulator of fat and glucose metabolism, dextran modulates blood sugar and lipids. Therefore, the enteral administration of dextran provides a convenient and simple way of selectively increasing the production of propionate in the gastro-intestinal tract and beneficially modulates physiologic parameters. Accordingly, administration of dextran provides a method for increasing insulin sensitivity. This is fully supported in the specification.

For example, the specification provides on page 1 at lines 21-25 that propionate, a short chain fatty acid, increases insulin sensitivity in addition to other physiologic parameters. This beneficial effect may be important/relevant in the nutritional management of conditions, such as diabetes, hypercholesterolemia and/or the like as disclosed in the specification on page 4 at lines 31-32. As the skilled artisan should understand, insulin sensitivity is reduced as insulin

resistance modulates triglyceride metabolism, that is, activates triglyceride-lipase activity freeing free fatty acids from the pool which again enhance insulin resistance.

Because insulin sensitivity is a measure for the effectiveness of removing glucose from the blood stream, Applicants respectfully submit that propionate as detailed on page 1 at lines 21-25 of the present application enhances glycolysis and inhibits gluconeogenesis both clear indicators of low blood glucose levels, thus again demonstrating the impact of propionate on glucose metabolism. As insulin is the only known molecule lowering blood glucose elevation, propionate may indirectly trigger a more effective way of absorbing glucose from the blood, and thus enhancing/increasing insulin sensitivity, which in turn may reasonably be understood as having an effect of lowering glucose levels of the blood. Moreover, propionate appears to mediate normalization of the blood glucose level in mammals. Thus, the claim term "increasing insulin sensitivity in a mammal" should be readily understood by the skilled artisan as further supported by the specification.

With respect to the enteral administration of a nutritional composition comprising dextran having a molecular weight above about 500,000 wherein dextran is administered in an amount from about 2g per day to about 15 g per day as claimed, Applicants believe that this is clearly enabled as further supported in the specification contrary to the Patent Office's position. For example, Example 3 provides the consumption of an acute dose of 15 grams Dextran T2000 and a chronic dose of 10g Dextran T2000 per day as disclosed in the specification on page 8 at lines 13-16. Further, Dextran T2000 is generally recognized in the art as dextran having a molecular weight of 2,000,000 where T2000 is generally recognized as an abbreviation of the molecular weight mass by the thousandth part. Therefore, Applicants believe that the claimed invention is clearly enabled as supported by the specification.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, paragraph 1 be withdrawn.

Applicants again note for the record that the Patent Office has not provided the Examiner's initials with respect to the reference entitled "Dietary Fructans, Roberfroid et al., Annu. Rev. Nutr., 1998, Vol. 18, pages 117-143 as referenced in PTO Form 1449 previously submitted by Applicants. Applicants believe that this reference was also submitted to the Patent Office at that time. Indeed, the Patent Office has not indicated otherwise. For convenience,

Applicants are submitting herewith another copy of this reference attached hereto as Exhibit B. Moreover, Applicants received a date stamped postcard further evidencing same, a copy of which is enclosed herewith as Exhibit C. Therefore, Applicants respectfully once again request that this reference be officially made of record and that the Patent Office provide Applicants with a copy of PTO Form 1449 with the Examiner's initials indicating same.

For the foregoing reasons, Applicants respectfully submit that the present application is in condition for allowance and earnestly solicit reconsideration of same.

Respectfully submitted,

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Dated: October 18, 2004

fecal samples (1 week intake of 10g per day)

C2: acetic acid
C3: propionic acid

Treatment

volunteer	propionate conc.	C3/C2	% propionic acid	**In average:**
1	89.89	-0.139	0.1	
2	- 13.73	-0.087	-2.7	
3	1.31	0.071	6.8	During treatment, propionate concentration increased by 24.0 µmol/g dry feces.
4	18.43	0.007	3.3	During treatment, propionate/acetate ratio decreased by 0.04.
av	**23.98 µmol/g dry**	-0.037	1.9	During treatment, %age of propionate on total SCFAs increased by 1.9%.

Placebo

volunteer	propionate conc.	C3/C2	% propionic acid	
1	11.39	-0.027	-0.7	
2	-2.35	-0.144	-4.6	
3	-27.51	-0.041	-0.9	During placebo, propionate concentration decreased by 5.7 µmol/g dry feces.
4	-4.36	-0.002	-0.2	During placebo, propionate/acetate ratio decreased by 0.05.
av	**-5.71 µmol/g dry**	-0.054	-1.6	During placebo, %age of propionate on total SCFAs decreased by 1.6%.

treatm-plac

volunteer		C3/C2	% propionic acid	
1	78.50	-0.112	0.8	
2	-11.38	0.057	1.9	
3	28.82	0.112	7.7	Relative to placebo, propionate concentration increased by 29.7 µmol/g dry feces.
4	22.79	0.009	3.5	Relative to placebo, propionate/acetate ration increased by 0.02.
av	**29.68 µmol/g dr**	**0.02**	**3.5**	Relative to placebo, %age of propionate on total SCFAs increased by 3.5%.

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JC20 Rec'd PCT/PTO 26 FEB 2002

In Re Patent Application of: **Jann et al.**

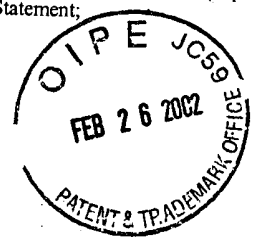
Serial No.: **09/979,533**

METHOD FOR INCREASING THE PRODUCTION OF PROPIONATE IN THE GASTROINTESTINAL TRACT

Docket No.: **112843-035**

On the date stamped hereon the U.S. Patent and Trademark Office hereby acknowledges the receipt of the following:

1. Transmittal of Information Disclosure Statement (duplicate);
2. Information Disclosure Statement;
3. PTO-1449; and
4. Cited References (6).



Mailed on: **January 9, 2002**

because of the absence of interfering components can be easily extracted and processed to purified products.

Inulin-Type Fructans and the Food Industry

In fact, three inulin-containing plant species are used in the food industry. In Mexico, over 20,000 ha of agave (*Agave azul tequilana*) are grown for the production of tequila. This national alcoholic drink is the distilled product of fermented inulin-containing agave juice. The inulin is converted to ethanol by a yeast species that grows naturally on agave (*Kluyveromyces marxianus*). The remaining two species currently used by the food industry to produce inulin belong to the Compositae: Jerusalem artichoke (*Helianthus tuberosus*) and chicory (*Cichorium intybus*), the later being by far the most commonly used source (23). In chicory inulin, both $G_{py}F_n$ (α-D-glucopyranosyl-[β-D-fructofuranosyl]$_{n-1}$-D fructofuranoside) and $F_{py}F_n$ (β-D-fructopyranosyl-[α-D-fructofuranosyl]$_{n-1}$-D-fructofuranoside) compounds are considered to be included under the same nomenclature, and the number of fructose units varies from 2 to more than 70 units (Figure 1). The presence of $F_{py}F_n$ compounds in native inulin extracts has

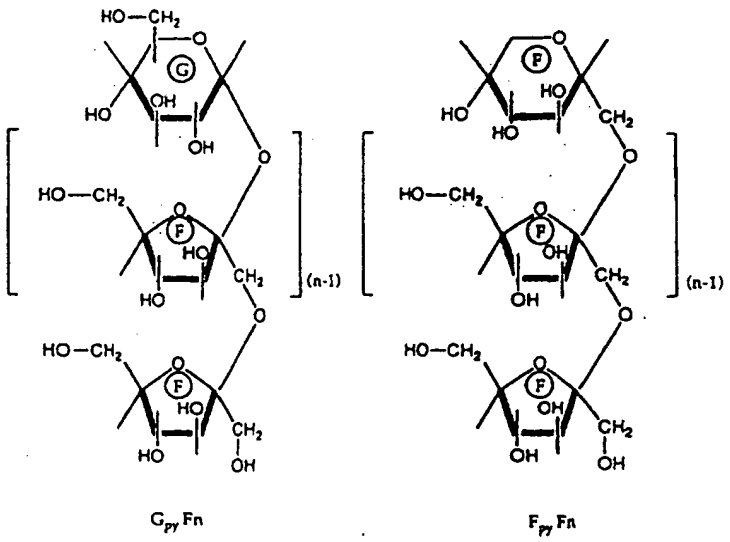


Figure 1 Chemical structure of $G_{py}F_n$ and $F_{py}F_n$ molecules in inulin-type fructans. *n* is the degree of polymerization or the number of β-D-fructofuranose; G and F stand for glucose and fructose, respectively; $G_{py}F_n$ is α-D-glucopyranosyl-[β-D-fructofuranosyl]$_{(n-1)}$-D-fructofuranoside; and $F_{py}F_n$ is β-D-fructopyranosyl-[D-fructofuranosyl]$_{(n-1)}$-D-fructofuranoside.

been demonstrated regularly with either gas chromatography or high-pressure anion exchange chromatography. Native chicory inulin (i.e. extracted from fresh roots, taking precautions to inhibit the plant's own inulinase activity as well as acid hydrolysis) has an average DP of 10–20. For native Jerusalem artichokes, the average DP is 6 (24). Even native inulin has a small degree of branching (approximately 1%) (25). The various fructose monomers in the $G_{py}F_n$ forms of inulin are all present in the furanose form. Only in the $F_{py}F_n$ forms is the reducing fructose in the pyranose form (23, 24, 25). Native inulin is processed by the food industry to produce either short-chain fructans, namely oligofructose (DP, 2–10; average DP, 5), as a result of partial enzymatic (endoinulinase EC 3.2.1.7) hydrolysis or long-chain fructans by applying industrial physical separation technique (24). In addition to chicory inulin and its hydrolysate, the food industry also produces a synthetic fructan that is a mixture of $G_{py}F_n$ oligomers in which n may vary from 2 to 4 (average DP, 3.6). Basically, they are sucrose molecules to which 1, 2, or 3 additional fructose units have been added by β-(2,1)-glycosidic linkage to the fructose unit of sucrose using the transfructosyl activity of the fungal enzyme β-fructosidase, from *Aspergillus niger* (18, 34).

Analysis of Inulin-Type Fructans

An analytical method has recently been developped to quantify inulin-type fructans in plants and food products (78). As a result of a multicenter validation ring test, this method has been adopted as the official method 997.08 of the Association of Official Analytical Chemists, which will be published in the 4th supplement (due out in 1998) to the *Official Methods of Analysis* (47). The method relies on the enzymatic treatment of the sample with an inulinase enzyme. Inulin-type fructans are extracted from the sample with boiling water. One aliquot is kept untreated as the initial sample. A second aliquot of the extract is hydrolyzed using an amyloglucosidase enzyme. A sample of the hydrolysate is analyzed and the rest is hydrolyzed using an inulinase (Fructozyme SP 230). Glucose, fructose, and sucrose are quantified in the three samples either by capillary gas chromatography, high-performance liquid chromatography, or, preferably, high-performance anion-exchange chromatography–pulse amperometric detection. The qualitative analysis of inulin-type fructans, in terms of content of the various oligomers ($G_{py}F_n$ and $F_{py}F_n$), can be performed on hot water extracts using the same chromatographic methods (24).

Inulin-Type Fructans as Dietary Carbohydrate

Inulin-type fructans are present in significant amounts in miscellaneous edible fruits and vegetables. The average daily consumption has been estimated to be 1–4 g in the United States and 3–11 g in Europe. The most common sources are wheat, onions, bananas, garlic, and leek (112). Chicory inulin

Table 1 Dietary fructans: name, origin, and chemistry[a]

Name	Origin	Chemistry	
		General formula	DP (n)
Inulins (INU)	Plant (*Cichorium intybus*)	$G_{py}F_n$	2–70 (average, 10–20)
Oligofructose (OFr)	Partial enzymatic hydrolysis of INU	$G_{py}F_n + F_{py}F_n$	2–10 (average, 5)
Synthetic fructan (SFr)	Enzymatic synthesis from sucrose	$G_{py}F_n$	2–4 (average, 3.5)

[a]DP, Degree of polymerization; n, number; INU, native chicory inulin; $G_{py}F_n$, α-D-glucopyranosyl-[β-D-fructofuranosyl]$_{n-1}$-D-fructofuranoside; $F_{py}F_n$, β-D-fructopyranosyl-[α-D-fructofuranosyl]$_{n-1}$-D-fructofuranoside; OFr, oligofructose produced by the partial enzymatic hydrolysate of chicory inulin; SFr, synthetic fructans produced by enzymatic synthesis from sucrose.

and oligofructose are officially recognized as natural food ingredients in most European countries and have a self-affirmed GRAS (generally regarded as safe) status in the United States; however, the synthetic fructans have been classified as a "novel food" (EU Regulation on Novel Foods and Novel Food Ingredients 258/97) by the ad hoc authorities of the European Commission. Inulin-type fructans are used as sugar substitutes, as fat replacers (inulin only), or for technological reasons (texturing agent, foam stabilizer, or improved mouth feeling) in miscellaneous food products (e.g. fermented dairy products; desserts such as jellies and ice creams; bakery products including biscuits, breads, and pastries; spreads; and infant formulas) (18). In a recent consensus paper (21), they have been classified as "nondigestible" oligosaccharides (28).

It is the aim of this article to review the scientific data demonstrating that inulin-type fructans positively affect various physiological functions in such a way that they can, or might in future, be classified as functional food ingredients for which health claims (functional claims or disease risk–reduction claims) might become authorized (83, 84). In this paper the following terminology is used: Inulin-type fructans is the whole family of compounds; native chicory inulin (INU) characterizes the native product extracted mainly from chicory roots but also possibly from Jerusalem artichoke; oligofructose (OFr) is the partial enzymatic hydrolyzate of INU; and synthetic fructans (SFr) identifies the fructans produced by enzymatic synthesis from sucrose (Table 1).

FATE OF INULIN-TYPE FRUCTANS IN THE GASTROINTESTINAL TRACT

Nondigestibility in the Upper Gastrointestinal Tract

Because of the β configuration of the anomeric C_2 in their fructose monomers, inulin-type fructans are likely to be resistant to hydrolysis by human digestive

enzymes (α-glucosidase, maltase-isomaltase, sucrase), which are specific for α-osidic linkages. As indicated above, inulin-type fructans have indeed been classified as nondigestible oligosaccharides (21, 28). Both in vitro and in vivo data support this classification.

Oku et al (73) reported that in vitro, SFr is not hydrolyzed to any significant extent by purified rat sucrase-maltase and does not compete with the natural substrates sucrose or maltose. However, using yeast invertase, Ziesenitz & Siebert (123) showed that GF_3 (nystose) is hydrolyzed at about 5% of the rate of sucrose and disappears completely within 2 h. When incubated in the presence of a homogenate of different segments (duodenum, jejunum, ileum) of rat or human small intestine, inulin-type fructans remain unchanged for up to 1 or 2 h (45, 65, 68, 123). In addition, because—as concluded by Nilsson et al (67, 68)—"the stomach hydrolysis of (inulin-type) fructans is likely to be of limited physiological significance," these products proceed undigested through the upper part of the gastrointestinal tract into the colon. That this is indeed the case has been confirmed by in vivo studies of rats (67, 68) and humans (4, 31, 65). The most convincing data are those of Bach Knudsen & Hessov (4) and Ellegärd et al (31). They used the ileostomy model, which provides a valuable alternative to the study of digestive physiology in man and which has often been used to quantify the small-intestinal excretion of nutrients, in particular the carbohydrates (20, 98). Both studies show that 86–88% of the ingested dose (10, 17, or 30 g) of INU and OFr are recovered in the ileostomy effluent, which supports the conclusion that INU and OFr are practically undigestible in the small intestine of man. The percentage recovery in the ileostomy effluent is of the same order as the recovery of pectin but slightly lower than that for cereal foods (32) and potatoes (98). Using an intubation technique in human volunteers, Molis et al (65) have similarly concluded that SFr is unabsorbed in the small intestine (89% recovery). The small but significant loss of inulin-type fructans during the passage through the small intestine could be due to fermentation by the microbial population colonizing the ileum, a population known to be up to 100 times greater in the ileostomists than in normal individuals (30). Bach Knudsen & Hessov (4) measured lactic acid and short-chain carboxylic acids, the end products of the anaerobic fermentation of carbohydrate, in the ileostomy effluents before and after INU intake, and they conclude that preferential fermentation of the fructans is a plausible explanation for the 12–14% loss in the small intestine. Another plausible explanation is acid and/or enzymatic hydrolysis of the low-molecular-weight fructans. Indeed, Oku et al (73), Nilsson & Björck (67), and Molis et al (65) have all shown that low-molecular-weight fructans are more sensitive to stomach and/or small intestinal hydrolysis than are the high-molecular-weight components.

Inulin-type fructans resist digestion in the upper part of the gastrointestinal tract; moreover, there is no evidence that they are absorbed to any significant extent (2, 65). Thus, it has been proposed that they may be classified as "colonic food," i.e. a "food entering the colon and serving as substrate for the endogenous bacteria, thus indirectly providing the host with energy, metabolic substrates . . ." (42).

FERMENTATION IN THE LARGE BOWEL: THE PREBIOTIC EFFECT The large bowel is by far the most heavily colonized region of the gastrointestinal tract, with up to 10^{12} bacteria for every g of gut content. Through the process of fermentation, colonic bacteria (most of which are anaerobes) produce a wide variety of compounds that may affect gut as well as systemic physiology. The fermentation of carbohydrates produces short-chain carboxylic acids (mainly acetate, propionate, and butyrate) and lactate, which allow the host to salvage part of the energy of nondigestible carbohydrates and which may play a role in regulating cellular metabolism as well as cell division and differentiation (for a review, see 19). Evidence that inulin-type fructans are fermented by bacteria colonizing the large bowel is supported by a large number of in vitro (both analytical and microbiological) and in vivo studies, which, in addition, confirm the production of lactic and short-chain carboxylic acids as end products of the fermentation. Furthermore, it has repeatedly been demonstrated that in human in vivo studies, this fermentation leads to the selective stimulation of growth of the bifidobacteria population, making inulin-type fructans the prototype prebiotic (40, 85, 88).

IN VITRO FERMENTATION OF INULIN-TYPE FRUCTANS The first line of evidence supporting the assumption that inulin-type fructans are fermented by the colonic microbiota is the demonstration that these carbohydrates are metabolized when incubated with human fecal samples in anaerobic batch cultures. Because such a fermentation is known to produce various acids, changes in the culture pH are easy proof of that assumption as well as—with pure cultures—an easy way to identify which bacteria have the potential to perform such a metabolic process. Moreover, by estimating the size of the drop in culture pH over a given period of incubation, it is also possible to compare different substrates on a semiquantitative basis. Such data have been reported for SFr by Hidaka et al (45, 46) and for INU and OFr by Wang (113), and they have been reviewed by Roberfroid et al (88). In summary, both INU and OFr are well fermented when incubations are performed using human fecal flora as inoculum, but the rate of fermentation of INU might be somewhat lower than that of OFr. By using the analytical methods described above to quantify INU and

OFr, it furthermore has been demonstrated that (*a*) both oligosaccharides are rapidly and completely metabolized by human fecal microflora, (*b*) the rate of degradation of the oligomers with a DP lower than 10 is approximately twice that of the molecules with a higher DP, and (*c*) $G_{py}F_n$- and $F_{py}F_n$-type components disappear from the culture media at a similar rate (88). In pure cultures, all strains of bifidobacteria, except *Bifidobacterium bifidum*, utilize inulin-type fructans, which are as good a fermentation substrate as glucose. However, when measuring growth rate (h^{-1}) of various pure cultures of bifidobacteria cultivated on either INU, OFr, or glucose, Wang (113) has shown that most bifidobacteria strains grow better on the former than on the later. Bacteria other than bifidobacteria that also have the potential to ferment inulin-type fructans, in pure batch cultures, include *Klebsiella pneumoniae, Staphylococcus aureus, Staphylococcus epidermis, Enterococcus fecalis, Enterococcus faecium, Bacteroides vulgatus, Bacteroides thetaiotaomicron, Bacteroides ovatus, Bacteroides fragilis, Lactobacillus acidophilus*, and *Clostridium* spp. (mainly *C. butyricum*) (45, 46, 88, 113). These studies show that except for a very few bacteria, the fermentability of OFr and SFr is comparable, but that in most cases INU is, among the three fructans, the least efficient fermentation substrate for bacteria other than bifidobacteria. When analyzing changes in the composition of both batch and chemostat cultures inoculated with human fecal slurries and INU or OFr, Gibson & Wang (39, 114) demonstrated that both inulin and its hydrolyzate selectively stimulate the growth of the bifidobacteria that at the end of the incubation become the predominant species (up to three orders of magnitude higher in numbers than the bacteroides). In vitro data demonstrate several facts: that inulin-type fructans are well fermented by human fecal slurries; that in pure cultures and among the bacteria known to be present in human feces, bifidobacteria, klebsiella, enterococci, bacteroides, and clostridia metabolize these carbohydrates; and that in mixed cultures, which mimic the real situation in the large bowel, the growth of bifidobacteria is selectively stimulated in such a way that these bacteria become largely predominant over the other populations.

IN VIVO FERMENTATION: THE PREBIOTIC EFFECT Inulin-type fructans have been used in volunteer studies with the aim of confirming, in vivo, the selective stimulation of the growth of bifidobacteria shown in vitro. The most complete studies with the best protocols have been reported by Gibson et al (39). They used adult subjects maintained on strictly controlled diets supplemented with 15 g of either OFr or INU per day, and they applied validated bacteriological methods to identify and count the major bacteria known to be present in the human feces, which moreover were collected anaerobically and cultured within a maximun of 30 min after sampling. These studies show that the intake of 15 g of OFr or INU per day significantly modifies the composition of the

fecal microbiota by stimulating the growth of bifidobacteria, which, after 2 weeks of such treatment, become by far the most numerous bacterial group. In addition, ingestion of OFr significantly reduces the count of bacteroides, fusobacteria, and clostridia. These effects last as long as OFr or INU continue to be consumed; however, after 2 weeks on the unsupplemented control diet, the composition of the fecal flora was still different from that of the control group, indicating that the changes disappeared progressively. Similar human studies in adult European, Japanese, and North American populations have been reported for inulin-type fructans using different daily doses (from 4 up to 40 g), but some of these studies report only the changes in the counts of bifidobacteria, thus questioning the selectivity of the effect (9, 11, 45, 46, 51, 64, 89, 117; E Menne, C Bila, N Guggenbul, J Absolonne, A Dupont, submitted for publication). The results of these studies are summarized in Table 2. As discussed previously (88), the analyses indicate that the dose-effect relationship is not straighforward. Whatever the dose of inulin-type fructans and whatever its nature (INU, OFr, or SFr), the number of bifidobacteria per gram of feces at the end of the feeding period is on the order of $10^{9.5}$. Moreover, the initial number of bifidobacteria in the feces, before supplementation of the diet with the fructan, may influence the size of the stimulation (the lower the initial count, the larger the stimulation) more than does the daily dose itself.

To summarize, both in vitro and in vivo studies on the fermentation of inulin-type fructans demonstrate that they are metabolized by anaerobic bacteria that are normal constituents of the colonic microbiota. But even if in pure cultures miscellaneous bacterial species have the capacity to use inulin-type fructans as

Table 2 Summary of the data showing in vivo the effect of inulin-type fructans on the counts of bifidobacteria in human feces[a]

Inulin-type fructan		Viable bifidobacteria per g of feces		Statistical significance	Reference
Compound	Dose (g/day)	Start of trial	End of trial		
SFr/$G_{py}F_n$	8	$10^{8.8}$	$10^{9.7}$	$P < 0.005$	64
SFr/$G_{py}F_n$	8	$10^{7.7}$	10^{9}	$P < 0.001$	89
SFr/$G_{py}F_n$	4	$10^{8.1}$	$10^{9.3}$	—	117
OFr/$G_{py}F_n$	15	$10^{8.8}$	$10^{9.5}$	$P < 0.001$	39
INU/$G_{py}F_n$	15	$10^{9.2}$	$10^{10.1}$	$P < 0.001$	39
SFr/$G_{py}F_n$	12.5	10^{8}	$10^{9.2}$	$P < 0.001$	9
SFr/$G_{py}F_n$	4	$10^{8.8}$	$10^{9.6}$	$P < 0.001$	11
INU/$G_{py}F_n$	40	$10^{7.7}$	$10^{8.9}$	$P < 0.001$	51
OFr/$G_{py}F_n$	8	$10^{8.6}$	$10^{9.6}$	$P < 0.001$	63

[a]SFr, Synthetic fructans produced by enzymatic synthesis from sucrose; $G_{py}F_n$, α-D-glucopyranosyl-[β-D-fructofuranosyl]$_{n-1}$-D-fructofuranoside; OFr, oligofructose produced by the partial enzymatic hydrolysis of chicory inulin; INU, native chicory inulin.

a fermentation substrate, in mixed cultures mimicking the large bowel as well as in vivo in human volunteers, these fructans have convincingly been shown to selectively stimulate the growth of bifidobacteria. They are thus bifidogenic and they classify as "prebiotics," i.e. "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or the activity of one or a limited number of bacteria in the colon and thus improves host health" (42).

PHYSIOLOGICAL EFFECTS IN THE GASTROINTESTINAL TRACT

Production of Short-Chain Carboxylic Acids and Related Effects

During their passage through the gastrointestinal tract, inulin-type fructans never produce fructose (73). Rather, their colonic fermentation produces short-chain carboxylic acids and lactate plus gases as products of their digestion. In doing so, only part of the energy of these dietary carbohydrates is salvaged, and consequently, they can be classified as a low-energy food ingredient. Indeed, their available energy content is only 40–50% that of a digestible carbohydrate, giving them a caloric value of 1.0–2 kcal/g (87). Concerning the pattern of production of short-chain carboxylic acids, unless very sophisticated studies of humans are done to measure the acids in situ and/or in the portal blood, it is impossible to know the pattern precisely. What is excreted in the feces is by no means representative of the in situ situation, because up to 95% of the acids produced in the colon are absorbed, probably in the ascending part of the colon. Data reporting an absence of modification of the fecal pattern of these acids in human volunteers fed inulin-type fructans are by no means relevant. Only in vitro fermentation and animal studies have been used to estimate the effect of nondigestible carbohydrates on short-chain carboxylic acids production. From animal in vivo studies, it can be concluded that supplementing diet with inulin-type fructans decreases the cecal pH and increases the size of the cecal pool of short-chain carboxylic acids, with acetate being the primary acid followed by butyrate and propionate. Moreover, butyrate is produced in higher concentration in fructan-fed than in control rats (12, 56, 80, 91, 120). Possibly related to this increase in the pool of short-chain carboxylic acids is the effect of inulin-type fructans on the intestinal tissue, leading to hyperplasia of the mucosa and increased wall thickness both in the small intestine (73) and in the cecum (12, 81). Moreover, this last effect is accompanied by an increase in blood flow (81). Additional effects of inulin-type fructans in the large bowel relate to the activity of either intestinal or bacterial enzymes [e.g. an increase in

cecal wall ornithine decarboxylase (81), an increase in bacterial β-fructosidase (9) and β-glucosidase (92), and a decrease (11, 92) or no effect (9) on bacterial β-glucuronidase but no effect on reductases (9, 11)], to the concentration of metabolites such as glycocholic acid (11) and NH_3 (92), which are both decreased, and to the mucins, in particular sulphomucin and sialomucin, which are decreased and increased, respectively (35). Moreover, because of the stimulation of bacterial growth leading to an increase in bacterial biomass, INU and OFr increase fresh fecal mass both in rats (87) and in humans (39).

Effect on Mineral Absorption

The nondigestible carbohydrates (dietary fiber) have regularly been accused of causing an impairment in the small intestinal absorption of minerals because of their binding/sequestering effect (49, 76, 95). But many studies have indicated that nondigestible carbohydrates per se do not affect mineral absorption or mineral balance (102), an effect that is more likely to be due to the presence of phytate or other mineral-complexing agents (96). However, the minerals that are bound/sequestered and, consequently, not absorbed in the small intestine reach the colon, where they may be released from the carbohydrate matrix and absorbed. Moreover, a high concentration of short-chain carboxylic acids resulting from the colonic fermentation of the nondigestible carbohydrates facilitates the colonic absorption of minerals, particularly Ca^{2+} and Mg^{2+} (108, 120). In addition, the presence of Ca^{2+} and Mg^{2+} in the colon may have important implications: it may help maintain colonic health by controlling the rate of cell turnover (6, 60), and high concentrations of Ca^{2+} in the colonic content may lead to the formation of insoluble bile or fatty acids salts, thus reducing the likely damaging activity of bile or fatty acids on colonic cells (115). Independent of any binding/sequestering minerals, some nondigestible carbohydrates (like the inulin-type fructans) may improve mineral absorption and mineral balance because of an osmotic effect that transfers water into the large bowel, thus allowing these minerals to become more soluble. In addition, being extensively fermented, they cause acidification of the colonic content and consequently raise the concentration of ionized minerals, in particular Ca^{2+} and Mg^{2+}, a condition that favors passive diffusion (17, 121).

That INU and OFr do not inpair mineral absorption in the small intestine has been reported by Ellegärd et al (31) in ileostomy patients. Indeed, these authors have demonstrated that the amount of Ca, Mg, and Fe ions recovered in the ileostomate over a 3-day period is not significantly modified after supplemention of the diet with 17 g of these fructans per day. Similarly, using double stable techniques, van den Heuvel et al (111) reported that in healthy adult, male volunteers, ingestion of 15 g of OFr per day interferes neither with Ca^{2+} nor iron ion absorption.

Using growing rats (both male and female), various groups have consistently reported that inulin-type fructans enhance Ca^{2+} and Mg^{2+} absorption (26, 29, 56, 71) as well as iron ions and Zn^{2+} balance without having a significant effect on Cu^{2+} bioavailability (27). These conclusions are based on mineral balance measurements, but some studies completed the analysis by measuring cecal enlargement and cecal concentration of calcium and magnesium salts (29, 56) or used more complex protocols, such as cecectomized rats, rats prevented from coprophagy to show that Ca^{2+} and Mg^{2+} absorption may be affected differently (3, 70, 72), or female ovariectomized rats to mimic the postmenauposal conditions (103). Doses of inulin-type fructans in the rat diet varied from 5% to 20%. The hypotheses most frequently proposed to explain this enhancing effect by inulin-type fructans on mineral absorption are (*a*) the osmotic effect; (*b*) acidification of the colonic content due to fermentation and production of short-chain carboxylic acids; (*c*) formation of calcium and magnesium salts of these acids; and (*d*) hypertrophy of the colon wall. But according to Ohta et al (70, 72), different mechanisms may be involved in the increased absorption of Ca^{2+} or Mg^{2+}, the former being absorbed mostly in the cecum and the latter mostly in the colon. In addition to improvement in Ca balance, Ohta et al (72) also reported that ingestion of SFr also increases calcium concentration in the femur. Similar positive effects on Ca^{2+} absorption have been reported for other nondigestible carbohydrates, in particular resistant starch (121).

More recently, and based on the consistently repeated observations in rats, in vivo human studies have been performed that confirm the positive effect of INU and OFr on the absorption and balance of dietary calcium but not of iron, magnesium, or zinc. In the first published report, nine men (21.5 ± 2.5 years) taking in ±850 mg of calcium/day and receiving a dietary supplement of 40 g of INU/day had a significant increase in the apparent absorption (±12%) and balance (+100 mg/day) of calcium without any change in urinary excretion (17). In the second study, 12 15- to 18-year-old boys consumed 16.8 g of OFr/day, and their calcium balance, measured by the double stable isotope technique, showed an 11% increase ($P = 0.09$), with no effect on urinary excretion (EGHM van den Heuvel, G Schaafsma, manuscript in preparation).

To summarize, inulin-type fructans are likely to affect positively calcium absorption and calcium balance, including in humans, without modifying urinary excretion. In animals, a similar effect has been reported for magnesium, iron, and possibly zinc, but it has not been confirmed in humans. The effect on Ca^{2+} bioavailability is probably due to both a transfer of calcium from the small intestine into the large bowel and an improved calcium availability in the colon as a result of the fermentation of the fructans.

Influence of Fructans on Glycemia/Insulinemia

The effects of inulin-type fructans on glycemia and insulinemia are not yet fully understood, and available data are sometimes contradictory, indicating that these effects may depend on physiological (fasting versus postprandial state) or disease (diabetes) conditions. OFr, given at the dose of 10% in the diet of rats for 30 days, reduces postprandial glycemia and insulinemia by 17% and 26%, respectively (53). However, the glycemic response during a glucose-tolerance test after overnight fasting is identical in control and OFr-fed rats (N Kok, personal communication). Furthermore, it has been reported that in rats fed 10% SFr for 3 months, the glycemic response to saccharose or maltose load is reduced, most probably as a result of a reduction of dissacharidase activity in the gastrointestinal tract (73). But in streptozotocin-treated (diabetic) rats, ingestion of a diet containing 20% OFr for 2 months decreases postprandial glycemia, despite a lack of modification of the glycemic/insulinemic response to a saccharose or maltose load (10). Similarly, chronic ingestion of SFr (20 g/day for 4 weeks) does not modify fasting plasma glucose and insulin in healthy human volunteers, even if it lowers basal hepatic glucose production (61). However, in diabetic subjects, taking 8 g of SFr/day for 14 days leads to a decrease in fasting blood glucose (119). Finally, when 10 g of artichoke INU was added to 50 g of wheat-starch meal in healthy human subjects, the blood glycemic response was lower, despite no apparent interference by INU on starch absorption (93).

There are two hypotheses to explain a possible effect of inulin-type fructans on the modulation of glycemia.

1. Even though they are not digested in the upper part of the gastrointestinal tract, inulin-type fructans may, like many other dietary fibers, influence the absorption of macronutrients, especially carbohydrates, by delaying gastric emptying and/or shortening small-intestinal transit time. Indeed, it has been reported that feeding rats a diet containing 10% and 20% SFr for 6 weeks shortens mouth-to-anus transit time by 25–50%, respectively. This suggests a dose-dependent effect (73, 109). It must be underlined, however, that inulin-type fructans do not have the high viscous effect other nonstarch polysaccharides have.

2. Inulin-type fructans may modify the hepatic metabolism of glucose, as is suggested by the lower fasting glycemia of normal subjects fed SFr (61). The reduced hepatic gluconeogenesis induced by fructans intake could be mediated by the short-chain carboxylic acids, especially propionate. Indeed, propionate given in the diet of rats for 4 weeks reduces fasting blood glucose

(7). Moreover, propionate inhibits gluconeogenesis in isolated hepatocytes, probably via its metabolic conversion into methylmalonyl-coenzyme A (CoA) and succinyl-CoA, both of which are specific inhibitors of pyruvate carboxylase (5). In addition, propionate enhances glycolysis, probably by depleting hepatic citrate, an allosteric inhibitor of phosphofructokinase. Finally, propionate may also influence hepatic glucose metabolism indirectly by lowering plasma fatty acids concentration, a factor known to be closely related to gluconeogenesis (55).

SYSTEMIC PHYSIOLOGICAL EFFECTS

Effect on the Metabolism of the Lipids

The effects of inulin-type fructans on triglyceridemia has been studied with both human subjects and animals (see Table 3 for summary). In rats, a decrease in serum triglyceridemia (in both the fed and fasted state) has consistently been reported in several studies (27, 33, 53). In healthy humans, however, only fasting triglycerides have been measured, and they are not modified (61, 74, 119)

Table 3 Influence of inulin-type fructans on serum lipids in animals and humans[a]

Subject	Type of fructans	Dose	Duration	Effects	Nutritional status	References
Animals						
Male Wistar rats	OFr	10% in diet	5 weeks	↓ total CHO ↓ total TG and VLDL-TG ↓ PL = HDL and LDL-CHO	Fasting	33
Male Wistar rats	OFr	10% in diet	4 weeks	↓ TG, ↓ PL = NEFA	Fed	28, 52
Male Wistar rats	OFr	20% in diet	5 weeks	↓ LDL-CHO, ↓ TG ↑ HDL-CHO	Fed	27
Male Wistar rats	INU	10% in diet	4 weeks	↓ TG	Fed	28
Rats	INU	10% in diet	5 weeks	↓ total CHO, ↓ TG = NEFA	Fed	73
Humans						
NIDD	SFr	8 g/day	14 days	↓ total and LDL-CHO = TG, HDL-CHO, NEFA	Fasting	119
Healthy	SFr	20 g/day	4 weeks	= TG, total and HDL-CHO = Apo A_1, ApoB, Lp(a)	Fasting	61
Healthy	INU	14 g/day	4 weeks	= TG, total-LDL and HDL-CHO	Fasting	74
Healthy	INU	9 g/day	1 month	↓ TG, ↓ total CHO = HDL	Fasting	13
Hypercholesterolemic	INU	18 g/day	3 weeks	↓ total and LDL-CHO = TG	Fasting	22

[a]OFr, Oligofructose produced by the partial enzymatic hydrolysis of chicory inulin; CHO, cholesterol; TG, triglycerides; VLDL, very-low-density lipoproteins; PL, phospholipids; HDL, high-density lipoproteins; NEFA, non-esterified fatty acids; INU, native chicory inulin; NIDD, non-insulin-dependent diabetic patients; SFr, synthetic fructans produced by enzymatic synthesis from sucrose. ↓, Decrease; =, no change; ↑, increase.

except in one study (13). No data have yet been published reporting studies performed with hypertriglyceridemic patients. Data concerning the effects of inulin-type fructans on cholesterolemia and/or lipoproteinemia are scarce.

EFFECT ON TRIGLYCERIDE METABOLISM Feeding rats a diet supplemented with OFr (10% in the diet) significantly lowers serum triglycerides and phospholipids concentrations (27), but it does not modify free fatty acid concentration in the serum. The hypotriglyceridemia is mostly due to a decrease in the concentration of plasma very-low-density lipoproteins (33). This effect is likely the result of a decrease in the hepatic synthesis of triglycerides rather than of a higher catabolism of triglyceride-rich lipoproteins (52, 53). Hepatocytes isolated from OFr-fed rats have a slightly lower capacity to esterify [^{14}C]palmitate into triglycerides and a 40% decreased capacity to synthesize triglycerides from [^{14}C]acetate (33, 53). These data support the hypothesis that a decreased de novo lipogenesis in the liver, through a coordinate reduction of the activity of all lipogenic enzymes, is a key event in the reduction of very-low-density lipoproteins–triglycerides secretion in fructans-fed rats. The fact that de novo lipogenesis is the basis for the hypotriglyceridemic effect of fructans in rat liver might explain the lack of effect observed in healthy humans, who eat far less carbohydrate than do rodents. Some experiments should be performed with either obese patients or insulin-resistant individuals eating high-carbohydrate–high caloric diets (1).

The hypotheses to explain a possible effect of inulin-type fructans on the modulation of triglycerides metabolism are indirect effects mediated two ways.

1. Through modifications of glucose and/or insulin levels, because dietary modulation of lipogenesis is often linked to such physiological changes. Indeed, the induction of lipogenic enzymes by glucose, occuring via an increased gene transcription, is potentiated by insulin (43). The association between glycemia/insulinemia and triglyceride has also been demonstrated for resistant starch, which, in rats, decreases serum triglyceride concentration, reduces fatty acid synthase activity by 20%, and concommittantly lowers postprandial insulinemia (104).
2. Through the production, in the large bowel, of short-chain carboxylic acids, leading to a more than twofold increase in the portal concentration of both acetate and propionate in OFr-fed rats (28). Moreover, propionate has been reported to inhibit fatty acid synthesis (59, 69, 118), whereas acetate is a lipogenic substrate.

EFFECT ON CHOLESTEROLEMIA The effect on cholesterolemia is controversial. SFr has been shown to lower serum total and low-density lipoprotein–cholesterol in non–insulin-dependent diabetic patients but not in healthy subjects (61, 119). Long-term (16 weeks) administration of OFr also decreases

total cholesterol level in the serum of rats (33). Ellegärd et al have shown that OFr influences neither the absorption of dietary cholesterol nor the excretion of cholesterol or bile acids in ileostomic subjects (31). The role of short-chain carboxylic acids in these effects is difficult to establish because, either in isolation or in mixture, these acids have antagonistic effects on cholesterol metabolism: Acetate, being a metabolic precursor of cholesterol, has been claimed to be at the origin of the hypercholesterolemia observed in healthy patients receiving lactulose (50), whereas propionate, which lowers serum cholesterol when added to the diet of rats, may decrease cholesterol synthesis, by inhibiting hydroxymethylglutaryl-CoA reductase (48, 90). Recently, preliminary data from slightly hypercholesterolemic human volunteers indicate that INU (18 g/d for 3 weeks) may lower both total and low-density lipoprotein serum cholesterol (MH Davidson, KC Maki, C Synecki, SA Torri, KB Drennan, submitted for publication).

Effect on Uremia and Nitrogen/Urea Disposal

Feeding rats a diet supplemented with INU and OFr (10%) for a few weeks decreases uremia, in both normal and nephrectomized rats (26, 122). Dietary INU effectively enhances fecal nitrogen excretion and reduces renal excretion of nitrogen in rats (121). This occurs because these fermentable carbohydrates serve as an energy source for the intestinal bacteria, which, during growth, also require a source of nitrogen for protein synthesis; however, it seems unlikely that inulin-type fructans exert any noticeable effect on protein digestibility in the small intestine (58). In addition, their osmotic effect in the small intestine accelerates the transfer of urea into the distal ileum and the large intestine, where a highly ureolytic microflora may proliferate. As a matter of fact, when fermentable carbohydrate intake is high, the amount of ammonia required to sustain maximal bacterial growth may become insufficient, and blood urea is then required as a ready source for bacterial protein synthesis in the cecum (107, 122). Besides its effect in the gastrointestinal tract and its possible role in modulating lipogenesis, propionate, an important end product of bacterial fermentation of inulin-type fructans, also inhibits ureagenesis in the liver in the presence of ammonia and amino acids. But whether such results (decreased uremia, shift of nitrogen excretion toward the colon) can be extrapolated to humans is questionable because of differences in digestive tract structure and colonic microflora. However, in humans, consumption of nondigestible carbohydrates also results in a higher fecal excretion of nitrogen (66, 100). In addition to increasing total nitrogen transfer to the colon, it is important to limit the formation of ammonia and various end products of protein catabolism, which have been proposed as causative risk factors for colonic carcinogenesis in the distal part of the large bowel (62).

DIETARY FRUCTANS AS FUNCTIONAL FOOD INGREDIENTS: POTENTIAL APPLICATIONS IN RISK REDUCTION OF DISEASES

Inulin-type fructans are either natural food ingredients (INU and OFr) or novel food ingredients (SFr). They have nutritional properties that, according to present scientific knowledge, originate mainly in resistance to the hydrolytic activities in the upper part of the digestive tract of monogastric organisms, followed by extensive fermentation in the large bowel, leading to an increase in bacterial biomass and, consequently, fecal mass. As extensively discussed previously (82), they have the key characteristics of dietary fibers, and a method has recently been approved by the Association of Official Analytical Chemists to include them in the analysis of complex carbohydrates (47). In addition, because they selectively stimulate the growth of bifidobacteria in the colonic microbiota, they are model prebiotics. Inulin-type fructans are obvious candidates to be recognized as functional food ingredients, for which health claims may become authorized (94).

Functional Food Ingredients: Definition, Strategy, and Health Claims

In general term, a functional food ingredient can be defined as "a food ingredient which affects physiological function(s) of the body in a targeted way so as to have positive effect(s) which may, in due course, justify health claims" (83, 84). A proposed strategy to develop the science base necessary to support such claims involves (*a*) the identification of the interaction(s) between the food ingredient and genomic, biochemical, cellular, or physiological function(s) in the body; (*b*) the demonstration of functional effect(s) in relevant experimental and human models; and (*c*) the investigation, in humans, of the consequence(s) of the functional effect(s), including effects on relevant biomarkers and possible health benefits.

Two different levels of health claims have tentatively been identified (84): (*a*) a functional claim, which refers to an effect on a specific or a limited number of genomic, biochemical, cellular, or physiological function(s) with no proven or fully understood relation to a particular disease (examples of such claims are bifidogenic effect, increased bioavailability of minerals, hypotriglyceridemic activity, stimulation of a particular immune function, etc); and (*b*) a disease risk–reduction claim, which refers specifically to effect(s) on the risk of a particular disease (examples of such claims are prevention of diarrhea or constipation, reduction of risk of carcinogenesis, cardiovascular disease, diabetes, obesity, etc).

This part of the review puts the basic and still mostly experimental scientific information currently available on the effects of inulin-type fructans on

both gastrointestinal and systemic functions into perspective regarding potential health claims.

Inulin-Type Fructans: Scientific Evidences for Functional Claims

Table 4 summarizes the available scientific evidence that supports or may be used to support functional claims. It also reports the critical assessment, by the authors, of these evidences in terms of strong, promising, or preliminary evidence.

The selective stimulation of growth of bifidobacteria in the colonic microbiota by inulin-type fructans is demonstrated both in experimental and in human studies. The scientific evidence for a bifidogenic effect of inulin-type fructans is thus strong, and it can be used to support an application for a functional claim, i.e. a modification of the composition of the colonic flora. Such a claim has already been officially cleared by the French Conseil supérieur d'Hygiène publique for food products containing OFr or Sfr. Even though the question of dose effectiveness is still debated, the dose-effect relationship for such an effect on a complex ecosystem like colonic microbiota may not be straightforward. It may depend on other factors, such as the initial number of bifidobacteria (88). This may lead to the conclusion that at the population level, the question of the dose is of low relevance and that, on an average base, taking into account the variability in the number of bifidobacteria in the human colonic flora, doses of a few grams per day are efficient in stimulating the growth of these bacteria classified as potentially beneficial for health (42). More important questions which remain to be answered are (*a*) the persistence of the bifidogenic effect,

Table 4 Scientific base for supporting functional claims for inulin-type fructans: state of the art and assessment of evidences[a]

Functional claims	Type of fructan	Science base		Assessment of evidences
		Experimental	Human	
Bifidogenic effect	INU, OFr, SFr	Yes	Yes	Strong
Fecal bulking via increased biomass	INU, OFr	Yes	Yes	Promising
Improved Ca bioavailability	INU, OFr	Yes	Yes	Promising
	SFr	Yes	No	Preliminary
Hypotriglyceridemic effect	OFr	Yes	?	Preliminary
	SFr	No	?	?
Hypocholesterolemic effect	INU, OFr	Yes	?	?

[a]INU, Native chicory inulin; OFr, oligofructose produced by the partial enzymatic hydrolysis of chicory inulin; SFr, synthetic fructans produced by enzymatic synthesis from sucrose.

both when keeping on a fructan-rich diet and when stopping consumption; (*b*) the interest, in terms of functional effects, of the so-called synbiotic approach, which combines fructans as a prebiotic and a probiotic strain (42), even if a first report shows no additional benefit of such a combination (8); and most importantly, (*c*) the health benefits of having a colonic flora in which bifidobacteria predominate (see below for a discussion on possible disease risk-reduction claims). An indirect consequence of the stimulation of growth of bifidobacteria is fecal bulking, for which promising evidences have been published (39, 87).

A second effect of inulin-type fructans that is worth considering when discussing potential functional claims is increased bioavailability of minerals. If data on the balance of Mg, Fe, or Zn are too preliminary yet to be taken into consideration, scientific evidence does exist to support effects on Ca. For INU and OFr, such an effect has been reported from both experimental animals and humans, and the evidence is assessed as promising. But for SFr, because only experimental data are currently available, the evidence is assessed only as preliminary. To the best of our knowledge, it is the first demonstration, including with humans, that a food component improves Ca bioavailability independent of Ca intake (17). Such a promising observation opens a new avenue for research and might have health implications if it is shown to contribute to reducing the risk of osteoporosis (see below for a discussion on possible disease risk–reduction claims).

The effects of inulin-type fructans on lipid metabolism are also discussed in this review. Experimental data are convincing in supporting the hypothesis that OFr inhibits hepatic lipogenesis in rat and, consequently, induces a significant hypotriglyceridemic effect. The potential mechanisms of this effect include metabolic effects of short-chain carboxylic acids and/or low glycemia/insulinemia. Except for one study, this hypolipidemic effect has not been confirmed with human volunteers consuming either INU or OFr. The evidence for an effect on cholesterolemia is scarce, both from the experimental model and from humans. When assessing these data, the authors concluded that preliminary evidence exists for an hypotriglyceridemic effect of OFr and possibly INU, but that it is impossible to conclude for their hypocholesterolemic effect as well as for the hypolipidemic effects of SFr. Because a metabolic link has recently been demonstrated between insulin resistance and the associated risk factors for atherosclerotic cardiovascular disease, especially hypertriglyceridemia, and because of the growing awareness that hypertriglyceridemia itself may be a risk factor in atherogenesis, these potential functional effects need to be carefully studied in humans, especially in conditions known to be associated with hyperinsulinemia and hypertriglyceridemia (1, 14, 16, 106) (see below for a discussion on possible disease risk–reduction claims).

Inulin-Type Fructans: Scientific Evidences for Disease Risk–Reduction Claims

For inulin-type fructans, disease risk–reduction claims are based on currently available scientific information and are only tentative; they need further research to be supported and validated. The most promising areas for the development of such claims are summarized in Table 5.

A last area for further research in the context of disease risk reduction by inulin-type fructans is cancer. Indeed, experimental data have been published recently that demonstrate that feeding rats inulin-type fructans significantly reduces the incidence of the so-called aberrant crypt foci induced by colon carcinogens such as azoxymethane or dimethylhydrazine (38, 54, 79, 92). For this particular effect, a synbiotic approach combining INU and bifidobacteria was shown to be more active than either the probiotic or the prebiotic alone (38, 92). Furthermore, Pierre et al (77) demonstrated that SFr reduces or even suppresses the number of tumors and stimulates the gut-associated lymphoid tissue (number of lymphoid nodules) in transgenic *Min* mice. Taper et al (105) reported that supplementing mice diet with INU or OFr slows down the growth rate of two different implanted tumors as compared with control rats. Fontaine et al (35) reported that in heteroxenic rats harboring a human colonic flora, INU stimulates the production of sulfomucin as well as a reduction in sialomucin, two effects known to be associated with a reduced risk of colon cancer (15, 97). In the strategy for functional food development described above, these cancer-inhibitory effects in experimental animals correspond

Table 5 Inulin-type fructans: tentative list of potential disease risk–reduction claims[a]

Determinant	Effect
Changes in colonic microflora	Relief of constipation
	Reduction of risk of intestinal infections
Modulation of lipid metabolism and/or insulinemia	Restoration of insulin sensitivity
	Reduction of risk of atherosclerotic cardiovascular disease
	Reduction of risk of obesity
	Reduction of risk of NIDD
Improved bioavailability of Ca^{2+}	Reduction of risk of osteoporosis
	Increased peak bone density
Others	Reduction of risk of colon cancer

[a]NIDD, Non-insulin-dependent diabetes.

to the first step, i.e. identification of effects that, because of their potential implications to human health, will need careful evaluation, including relevant human studies.

CONCLUSIONS AND PERSPECTIVES FOR FOOD APPLICATIONS

As discussed recently (21), dietary carbohydrate is a large family of miscellaneous compounds with different physiological effects and different nutritional properties that deserve much attention from nutritionists. Among the carbohydrate family, the nondigestible oligosaccharides have been shown to be of particular interest, and they may, in the next decade, be one of the most fascinating functional food ingredients. The inulin-type fructans are the nondigestible oligosaccharides for which a wide range of scientific data are already available that demonstrate an array of potential health benefits. To justify functional or disease risk–reduction claims, most of these data will have to be confirmed in humans through relevant nutrition studies focusing on well-validated end points. Such studies will be of much value if they rely on sound mechanistic hypotheses. Changes in the composition of the colonic microbiota, modulation of the metabolism of triglycerides, modulation of insulinemia, improved bioavailability of dietary Ca, and negative modulation (86) of colon carcinogenesis appear to be the most promising areas for further research.

Besides their nutritional properties, which may, in due time, justify their classification as functional food ingredients, inulin-type fructans are also low-calorie carbohydrates (87). These have been shown to have interesting technological properties in food product development. Although the nutritional effects are not, these technological properties are dependent on the molecular structure of the various inulin-type fructans, especially their degree of polymerization, which determines their water solubility, their viscosity, their water retention capacity, and their capacity to form a cream-like texture, a property of INU, which makes it a good fat replacer (36).

As with all other nondigestible carbohydrates that have osmotic properties and are extensively fermented in the large bowel, inulin-type fructans may cause intestinal discomfort or even function as a laxative (at very high daily doses). However, both the occurrence and the intensity of these effects are clearly dose related and depend on the daily regimen of intake, and they may vary significantly from one individual to another. Based on the published data (44, 74, 75, 101), the following conclusions can be drawn: in a liquid food product, a single daily dose of 10 g will not cause a transient appearance of mild symptoms of intestinal discomfort, whereas a single daily dose of 20 g may,

and the single daily dose likely to cause major discomfort in most individuals (except very resistant high-fiber consumers) is 30 g. However, if the dose is split through the day into several individual servings, symptoms of discomfort will be reduced and, in most cases, will disappear, even for total daily doses as high as 20–30 g. Liquid food products containing inulin-type fructans are always more likely to induce intestinal discomfort than solid formulations are, and the risk of an effect is reduced if the food product is consumed as part of a complete meal. Finally, it must be underscored that a small percentage (1–4%) of the population might have a higher-than-average sensitivity to these intestinal discomforts. But these highly sensitive individuals are also likely to be very sensitive to the intestinal discomfort caused by sugar alcohols, any nondigestible carbohydrates, or even fermented dairy products.

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ABSTRACT

Fructan is a general term used for any carbohydrate in which one or more fructosyl-fructose link constitutes the majority of osidic bonds. This review focuses on the fate of inulin-type fructans (namely native chicory inulin, oligofructose produced by the partial enzymatic hydrolysis of chicory inulin, and synthetic fructans produced by enzymatic synthesis from sucrose) in the gastrointestinal tract, as well as on their systemic physiological effects on mineral absorption, carbohydrate and lipid metabolism, hormone balance, and nitrogen homeostasis. The scientific evidence for the functional claims of inulin-type fructans is discussed, as well as their potential application in risk reduction of disease, namely constipation, infectious diarrhea, cancer, osteoporosis, atherosclerotic cardiovascular disease, obesity, and non-insulin dependent diabetes.

CONTENTS

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INTRODUCTION

Definition, Chemistry, and Biosynthetic Pathways

Fructan is a general name used for any carbohydrate in which one or more fructosyl-fructose link constitutes the majority of osidic bonds. Fructans are linear or branched fructose (oligo)polymers, which are either β-2,1-linked inulins or β-2,6-linked levans. Inulin has been defined as a polydisperse carbohydrate material consisting mainly, if not exclusively, of β-(2-1) fructosyl-fructose links. It is mainly of plant origin, whereas some fungi and many bacteria are the major producers of levans (37, 116). Because they are synthesized from sucrose, by repeated fructosyl transfer from a fructosyl donor, both inulins and levans usually, but not always, have a terminal glucose unit. Indeed, the enzymes generally considered to be involved in plant fructans synthesis are sucrose-sucrose fructosyltransferases (EC 2.4.1.99), which catalyze fructosyl transfer from one sucrose molecule to another, leading to 1-kestose (glucosyl-1,2-fructosyl-1,2-fructose). Chain elongation is mediated by either 1^F- or 6^F-fructan-fructan-fructosyltransferase (EC 2.4.1.100), leading to inulins and levans, respectively. Fungal and bacterial inulins and levans are generally assumed to be synthesized without a trisaccharide as intermediate, but by sequential transfer of fructosyl residues from sucrose as fructosyl donor to the growing inulin and levan chains by inulosucrase (sucrose 1^F-fructosyltransferase) and levansucrase (sucrose 6^F-fructosyltransferase), respectively (99). They have a much higher degree of polymerization (DP) (up to 100,000) than plant inulin (DP up to 150).

Plant Sources

Fructan-containing plant species are found in a number of mono- and dicotyledonous families, such as Liliaceae, Amaryllidaceae, Gramineae, and Compositae. Parts of various fructan-containing plant species are often eaten as vegetables (e.g. asparagus, garlic, leek, onion, artichoke, Jerusalem artichoke, scorzonera, chicory roots, etc) (112). However, only a limited number of species are suitable for industrial food and non-food application (37). Despite the high fructan content of the aerial parts of many Gramineae, particularly of young seedings (up to 70% of their dry weight), grasses and cereals do not lend themselves to industrial extraction and processing of fructans. Conversely, in Liliaceae, Amaryllidaceae, and Compositae, fructans (most exclusively inulins) are usually stored in organs such as bulbs, tubers, and tuberous roots, which